February 18, 2020

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U.S. Environmental Protection Agency
EPA Docket Center
Mail Code 28221T
1200 Pennsylvania Avenue NW
Washington, DC 20460

Re: EPA Proposed Amendments to "National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Source Category" Docket ID No. EPA-HQ-OAR-2018-0746 (84 Fed. Reg. 242; Dec 17, 2019)

To Whom It May Concern:

The Ethylene Oxide Panel of the American Chemistry Council (EO Panel), hereby submits comments on the proposed amendments to the "National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Source Category" (MON). Our comments focus on amendments pursuant to the risk review that specifically address ethylene oxide (EO) including the following:

- MON Section IV. C. 3. **Determination of Risk Acceptability** (proposed MON amendment)
- Memorandum referenced in Section IV.C.3: **Sensitivity of Ethylene Oxide Risk Estimates to Dose-Response Model Selection.** 18 October 2019 from Paul White to Kristina A Thayer (ORD, 2019)

The MON proposal requests additional comments on the use of the 2016 updated unit risk estimate (URE) for ethylene oxide for regulatory purposes beyond those already submitted for the HCl Production RTR proposed rule as well as comments on the use of an alternative URE for ethylene oxide in the final rule for this source category. For reference, we attach the EO Panel's previous submissions, including its Information Quality Act Petition (2018), comments on the proposed HCL production RTR (HCL RTR, 2019), and comments on the Texas Commission on Environmental Quality's draft Decision Support Document for EO (2019).

The draft MON refers to the alternative URE proposed by TCEQ which was issued in June, 2019. We strongly support the scientific approach used by TCEQ to derive an alternative URE because it emphasizes biological plausibility and mode of action as guiding principles.

Although this TCEQ (2019) alternative approach is different from that previously submitted by the EO Panel (2019) in comments on the proposed HCl RTR, they have in common the use of the Cox proportional hazard (CPH) model. The EO Panel recommended approach makes use of all the available data from the two strongest cohorts. The TCEQ (2019) approach is based on the same cohort and lag period selected by IRIS (2016). Table 1 presents two alternative URE's that include a new EO Panel Alternative (URE #1) based on the TCEQ (2019) proposed URE with the age-dependent adjustment factor (ADAF) in a manner similar to the approach used by IRIS (2016), and the previously proposed Alternative (URE #2) based on the Valdez-Flores et al. (2010) described in detail in our comments on the proposed HCl RTR.

Table 1. Comparison of IRIS (2016) and ACC Proposed Alternative URE

	IRIS (2016)	New ACC Alternative 1	Alternative 2 (ACC,2019 HCl RTR)
Cohort	NIOSH Human	NIOSH Human	NIOSH and UCC Human
Critical endpoint	lymphoid incidence (based on mortality data[1]) in males and females and breast cancer incidence in females	lymphoid mortality in males and females and males alone	lymphoid mortality in males alone
Model	2-piece linear spline	Cox proportional hazard	Cox proportional hazard
Lag Period	15 yr	15 yr	0 lag
ADAF method	IRIS approach apply 1.66 factor to slope	IRIS approach apply 1.66 factor to slope	EPA (2005) cancer guidelines approach for each age[2]
Point of departure	LEC 1/100	LEC 1/100,000[3]	LEC 1/1,000,000[4]
URE (per $\mu g/m^3$)	5.0 E-03	2.3E-06	5.0 E-07
1/M RSC ($\mu g/m^3$)	0.00018	0.44	0.92
1/M RSC (PPT)	**0.1**	**245**	**500**

[1]Steenland et al. (2004) only published mortality data. IRIS (2016) incorrectly applied the upper bound on the slope for cancer mortality together with background incidence rates in a life-table calculation of the excess risk to estimate lymphoid incidence (detailed explanation provided in Sielken and Valdez-Flores (2009a).
[2]Sielken and Valdez-Flores (2009b) for method used for ADAF for cumulative exposures according to EPA (2005) guidelines
[3]IRIS did not provide justification for selection of point of departure of 1/100. In contrast, this report demonstrates that an LEC 1/100,000 is within the experimental range of cumulative exposures associated with cases of lymphoid mortality and more consistent with EPA's recommendations for point of departure.
[4]1/1,000,000 was determined to be within the exposure range of individuals in the cohorts combined.
[5]Based on URE proposed by TCEQ (2019) multiplied by an ADAF factor of 1.66.

In 2016, the EPA IRIS selection of the supralinear 2-piece spline model gave rise to one of the highest cancer potency estimates among those previously derived by IRIS (Figure 1). The EO Panel presents evidence here that this model is not justified based on

the relatively weak epidemiological findings reported by Steenland et al. (2003, 2004) and the weight-of-evidence in the epidemiological literature (Marsh et al. 2019). The IRIS (2016) URE for EO results in a 1 in a million extra risk specific concentration (1/M RSC) for EO of 0.1 ppt, which is highly implausible based on epidemiological, toxicological and biological mode-of-action evidence. IRIS (2016) considered an unprecedented number of statistical models each with different permutations of lag times, exposure metrics and, in the case of the spline models, multiple positions of the knot. The selection of the model was based almost exclusively on statistical analysis and visual fit, without any check against the observed data or consideration of biological plausibility.

In this submission, the EO Panel provides new figures and analysis of the observed epidemiology data to illustrate that the CPH model is more consistent with the dose-response form of the epidemiological, toxicological and biological mode of action. Our comments also include scientific rationale for selecting lymphoid mortality as the critical endpoint for quantitative cancer risk.

The proposed MON relies on the ORD (2019) memo that includes a sensitivity analysis evaluating a range of alternative risk values, concluding that the IRIS URE values could have been up to 5 times lower. The MON includes a range of possible values for cancer risk. We agree with considering a range of values including central estimates, but the ORD memo ignored a more standard statistical model—a CPH model—that has a comparable statistical and visual fit to the one selected by IRIS[1]. More importantly the CPH model has greater biological plausibility, fitting the EPA SAB (SAB, 2015) selection criteria for models, which has been discussed in detail in our previous comments.

This ORD (2019) sensitivity analysis rejects the CPH model (for cumulative exposures), which is the model that has a dose-response form that is both biologically plausible and more consistent with the observed data. This is the same model used in derivation of alternative values by TCEQ (2019) and ACC (2019). Instead ORD (2019) includes a linear regression of the categorical data, which the SAB (2015) specifically rejected because it was based on categorical results instead of the continuous individual-level exposure data. Thus, the ORD (2019) memo "stacks the deck" by excluding consideration of the CPH model that has much greater biological plausibility and is much more reflective of the relatively weak epidemiological findings reported by the original authors.

[1] TCEQ (2019 table 38) calculates correct p-value = 0.14 for IRIS selected 2-piece spline. Thus both the IRIS selected 2-piece spline model and CPH models are not statistically significant. Despite the lack of significance for an exposure-response relationship, a conservative yet scientifically sound alternative approach is to calculate extra risk using the CPH model. The CPH model becomes the model of choice because it is a more parsimonious (simpler) model, has greater biological plausibility, and predicts the observed lymphoid mortalities in the NIOSH study compared to the IRIS selected 2-piece spline model..

Our previous comments indicate that if a more standard CPH model is applied using cumulative exposures, the IRIS URE should be 3 orders of magnitude (e.g. more than 1000-fold) lower than the IRIS value (Table 1) not just 3-5 fold lower. The CPH model was rejected based on a subjective visual fit by ORD (2019). As indicated in our previous comments, a major flaw with this approach is that it relies on comparing models with very few (4-10) categorical odds ratio data points that are not representative of the larger individual data modeled (53 lymphoid, 233 breast cancer cases). We provide new information and graphical presentation on the exposure-response pattern to show that the steep exposure-response at low exposures is not consistent with the observed data and conclusions published by Steenland et al. (2003, 2004). Unfortunately, these misleading figures were the basis for the SAB and IRIS (2016) to incorrectly conclude that spline models are a better local fit in the low exposure range.

A superior approach to assessing model fit is to calculate the number of cases predicted by the model rather than relying on subjective "eyeballing" of the data. TCEQ (2019) used more objective methods to show unequivocally that the CPH model predicts the cases accurately, while the IRIS selected 2-piece spline model overestimates the spline 95% of the time. This TCEQ evaluation of the model fit is a true reflection of model fit to the observed data prior to any additional conservative assumptions IRIS applied to the model.

The ORD memo points out (at p. 6) that "It is important to note that this analysis relies entirely on results and equations presented in the final EO IRIS assessment", and thereby makes it clear that it did not independently evaluate IRIS (2016) statistical analysis or consider TCEQ's peer review of the IRIS analysis. The proposed MON rule notes the concerns raised by TCEQ but appear to dismiss them by claiming that the proposed TCEQ assessment has not been peer reviewed[2]. However, TCEQ points out a very simple statistical error- IRIS (2016) did not account for all three instead of just two parameters that were numerically optimized for all spline models[3]. The mistake of omitting a single degree of freedom led IRIS (2016) and ORD (2019) to mischaracterize the supralinear 2-piece spline model fits as being adequate while rejecting the CPH model.

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[2] The MON (2019) states: "TCEQ highlighted uncertainties in the URE arising from what it considered to be errors in the assumptions and calculations used to determine the best model fit on the data. TCEQ's concerns with the EPA's URE derivation have not been peer reviewed and the public comment period closed on September 26, 2019." Fed Reg 2019 (Tues Dec 17); 84 (242):69218

[3] The SAS statistical software used by IRIS required the user to ensure that a correct number of estimated parameters is entered into (or assumed by) that program when fitting a model to data. In the case of 2-piece spline model fits, the parameters representing the two slopes and the X-axis value of the "knot" or point of intersection that connects those two slopes).

The simple statistical error documented by TCEQ is not the type of claim that requires peer review to be valid. It is a basic principle clearly stated in the National Research Council report entitled "Models in Environmental Regulatory Decision Making", which states that the strategy to pick the "best model" for regulatory decision making should be "*subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters versus having a parsimonious description*" (NRC, 2007, pp. 174). The EO Panel provides new information revealing that IRIS (2016) incorrectly claims the SAB approved this apparent violation of basic statistical principles.

We bring to light an analysis by IRIS (2016, Appendix D) estimating p-values with and without including the parameter for the knot suggesting awareness of this issue. **The fact that a simple statistical error of omitting a single degree of freedom can result in a three orders of magnitude difference in EO cancer potency emphasizes the tenuous basis of any EPA rule, such as the MON, that relies on the IRIS (2016) EO cancer assessment[4].**

The MON also importantly notes the SAB advice that model selection should have a "dose-response shape that is… biologically plausible" (MON, footnote 39). In this context, as an important dose perspective, our bodies produce EO through normal metabolic processes at levels that are approximately equivalent to inhalation of 1,900 ppt ± 1,300 ppt (Kirman and Hays, 2017). The IRIS (2016) stated that "it is *highly plausible* that the dose-response relationship *over the endogenous range* is sublinear" [emphasis added]. The basis for this conclusion was described in our comments on the HCL RTR.

Briefly, EO molecular and tissue injury is moderated at low EO exposures by overlapping biological defenses. These new comments add additional information that demonstrate that none of these biological defenses are plausibly expected to be saturated at low EO exposures. These data further indicate that it is highly biologically implausible that the contribution of an additional 0.1 ppt exogenous EO to an existing 1,900 ppt background endogenous EO exposure, would result in a sudden and biologically unexplained shift to a supralinear exposure response and mode of action. This is particularly so considering that such an additional minute exogenous EO exposure is also a very small fraction of the reasonable variability range of normal human endogenous background EO exposures (1,300 ppt). We provide further evidence supporting the conclusions of Kirman and Hays (2017) that the standard deviation reflects expected biological variation and not experimental variation.

[4] See footnote 1 on page 3 for further details

The biological plausibility of a low-dose supralinear dose response is also inconsistent with animal toxicology and mode of action data for EO. Of particular importance is that ethylene is not carcinogenic in rats despite producing an approximate 3 ppm EO equivalent dose at the top 3,000 ppm ethylene tested exposure. The IRIS supra-linear EO dose response incorrectly projects the ethylene bioassay should have been positive. The biological plausibility of the EPA hypothesized low-dose supra-linear dose response is inconsistent with the observation that doses of EO in rats did not increase DNA adducts, the molecular-initiating mode of action target of EO-induced cancer, at approximately 4 orders of magnitude greater than the dose in a human exposed to 0.1 ppt EO (Marsden et al., 2009).

To summarize, the proposed MON relies on the ORD (2019) sensitivity analysis which is based on the IRIS (2016) incorrect statistical modeling and misleading visual fit. Our detailed comments elaborate on these points.

I. The proposed MON is based on the ORD (2019) visual fit comparisons to categorical data, which misrepresents the individual data modeled. This flawed visual fit as the basis for the IRIS (2016) selection of a spline model leads to deriving one of the highest inhalation UREs.

II. The ORD (2019) memo did not make a simple correction in statistical analysis that led to an incorrect conclusion that the 2-piece spline model has superior fit compared to the CPH model. Because the ORD memo—cited as a key basis for the proposed MON rule—is flawed, so is the dose-response analysis on which the proposed rule is based.

III. The ORD (2019) sensitivity analysis does not consider biological plausibility and consistency based on the results of the epidemiological studies. The overall weak findings suggest a shallow and not a steep exposure response at low exposures, and do not support derivation of one of the highest inhalation URE's.

IV. Lymphoid morality in humans is an appropriate health outcome for risk assessment, as is, without transformation to incidence. The overall weak findings of the lymphoid mortality data suggest a shallow and not a steep exposure response at low exposures.

V. Although useful for consideration of the overall weight-of-evidence, breast cancer should not be considered a critical cancer endpoint for quantitative risk assessment purposes based on the lack of robust findings in Steenland et al.

(2003, 2004) and weight-of-evidence in the epidemiological literature. The breast cancer incidence data should not be used for quantitative risk assessment purposes based on substantial under-ascertainment of cases reported by Steenland et al (2003) and compounded by risk deficits in the lower exposures.

VI. IRIS (2016) did not consider the biological plausibility of models based on the biological mode of action and toxicological evidence, which support a shallow linear exposure-response at lower exposures. IRIS has not offered any biologically plausible mode of action analysis accounting for a supralinear dose-response of EO in the low-exposure range. In contrast, considerable experimental mode of action data consistently indicate it is highly implausible that EO operates by supralinear exposure response in the exposure region estimated by IRIS as increasing cancer risks.

VII. The ACC alternative proposal for URE is conservative and has a dose-response form that is both biologically plausible and consistent with the observed data. The rationale for selection of the critical endpoint and point-of-departure are summarized.

EPA must revise its risk modeling and analysis by using a unit risk estimate (URE) value for EO that is scientifically justified instead of relying on the 2016 Integrated Risk Information System (IRIS) value. The IRIS value is an incorrect and overly conservative value based on implausible exposure-response models and flawed exposure assessments. We strongly encourage EPA to consider all of the available alternatives to the EO IRIS value for regulatory uses. Thank you.

Sincerely,

William Gulledge

William P. Gulledge
Senior Director
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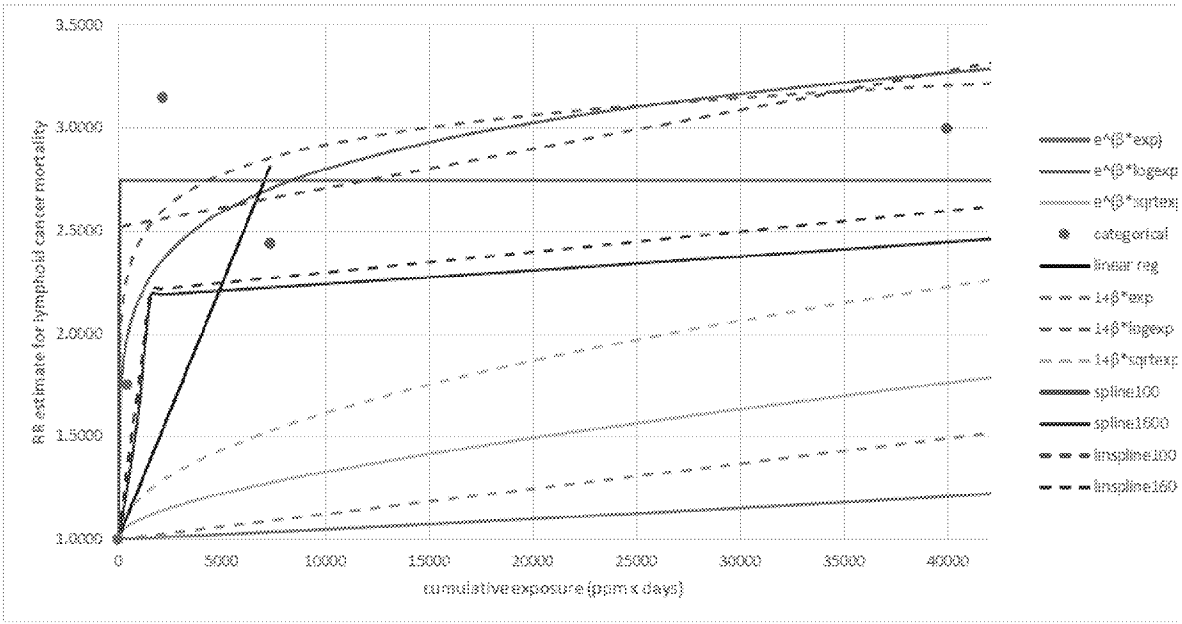
I. The proposed MON is based on the ORD (2019) visual fit comparisons to categorical data, which misrepresents the individual data modeled. This flawed visual fit is the basis for the IRIS (2016) selection of a spline model leading to the derivation of one of the highest inhalation UREs.

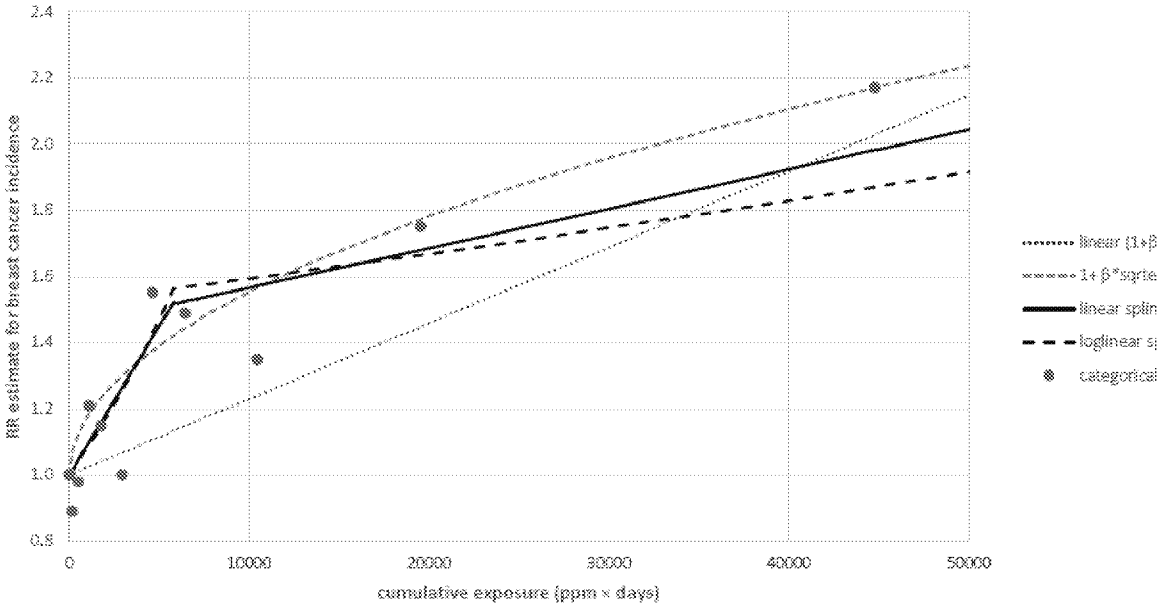
Steenland et al. (2003, 2004) calculated four to ten odds ratios (ORs), which uses worker to worker comparisons within the study. These odds ratios play a major role in the derivation of a very high URE because ORD (2019) and the IRIS (2016) both use very few odds ratios to determine which continuous models (e.g. 2-piece spline vs. CPH) have acceptable "local fit" at the lower exposure levels based on subjective visual comparisons. Figures 1 and 2 are identical to Figures 4-3 and 4-8 from the IRIS (2016), which use the grouped "categorical" odds ratio data (solid purple points) to compare the visual fits of the different models. These figures (Figures 1 and 2) give the false impression of a very clear dose response pattern when confidence intervals (CI) are not added. The same categorical data with CIs are shown first on the same y-axis linear scale as the IRIS figures (Figures 3 and 4), and then on a log scale (Figures 5 and 6).

Figure 1 IRIS (2016) Figure 4-3: Odds ratio for quartiles (closed circles) for lymphoid cancer mortality (with 15 year lag)



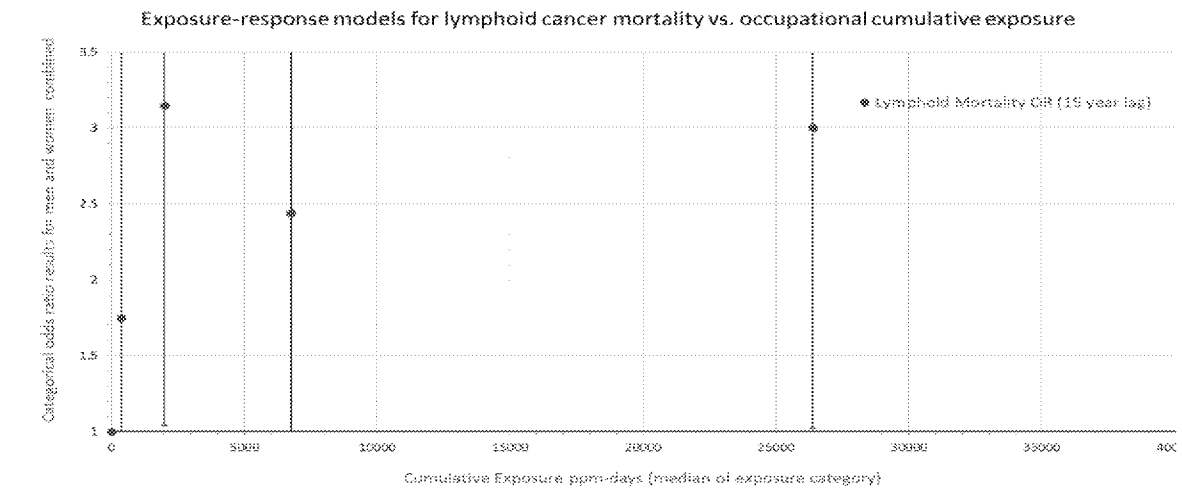
The red dashed line is the 2-piece spline model with knot at 1600 ppm-days selected by IRIS. The solid blue line is the CPH model proposed in this report and published by Steenland et al. 2004. Note: IRIS states that the various models are not comparable along the y-axis.

Figure 2 IRIS (2016) Figure 4-8: Odds ratio for deciles (closed circles) for breast cancer incidence in subcohort with interviews (with 15 year lag)



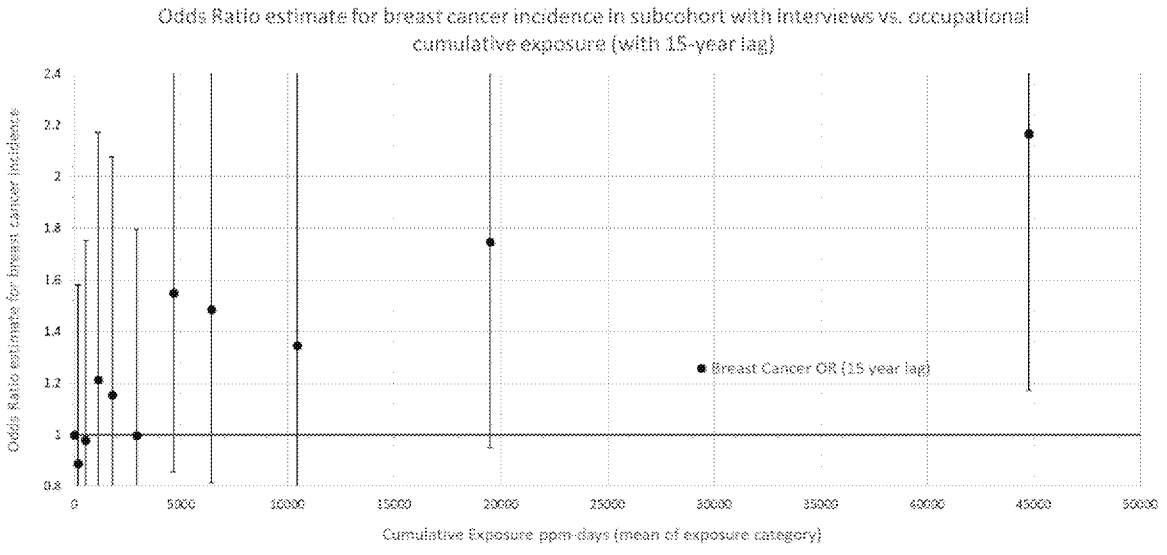
The black solid line is the 2-piece spline model selected by IRIS. IRIS did not plot the CPH model for this subcohort with interviews, but it would be flatter than the red dotted line. Note: IRIS states that the various models are not comparable along the y-axis.

Figure 3 Odds Ratio for Lymphoid Mortality (15 year lag) with same y-axis linear scale as IRIS (2016) figures used to determine visual fit (Odds ratio and 95% confidence interval).



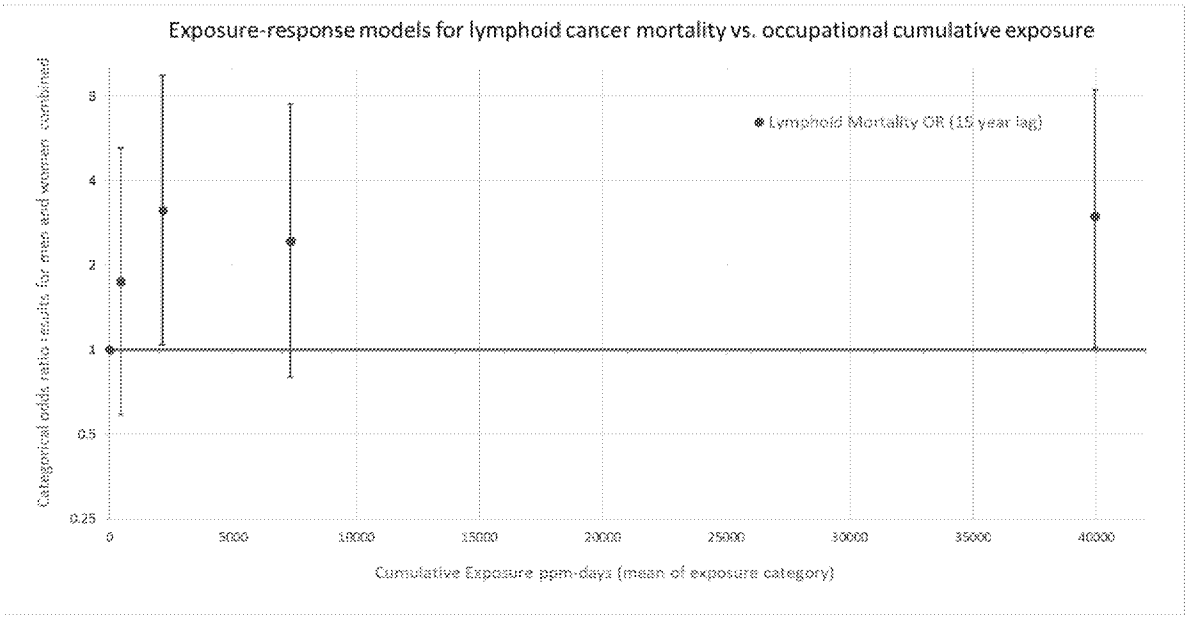
Data from IRIS (2016) Tables D-26 and D-28. ORs with confidence intervals indicate exposure response is not supralinear. Medians of exposure category were reported and are considered superior to mean values. ORs with CIs that do not include 1 are statistically significant.

Figure 4 Odds Ratio for Breast Cancer Incidence (15 year lag) with same y-axis linear scale as IRIS (2016) figures used to determine visual fit (Odds ratio and 95% confidence interval).



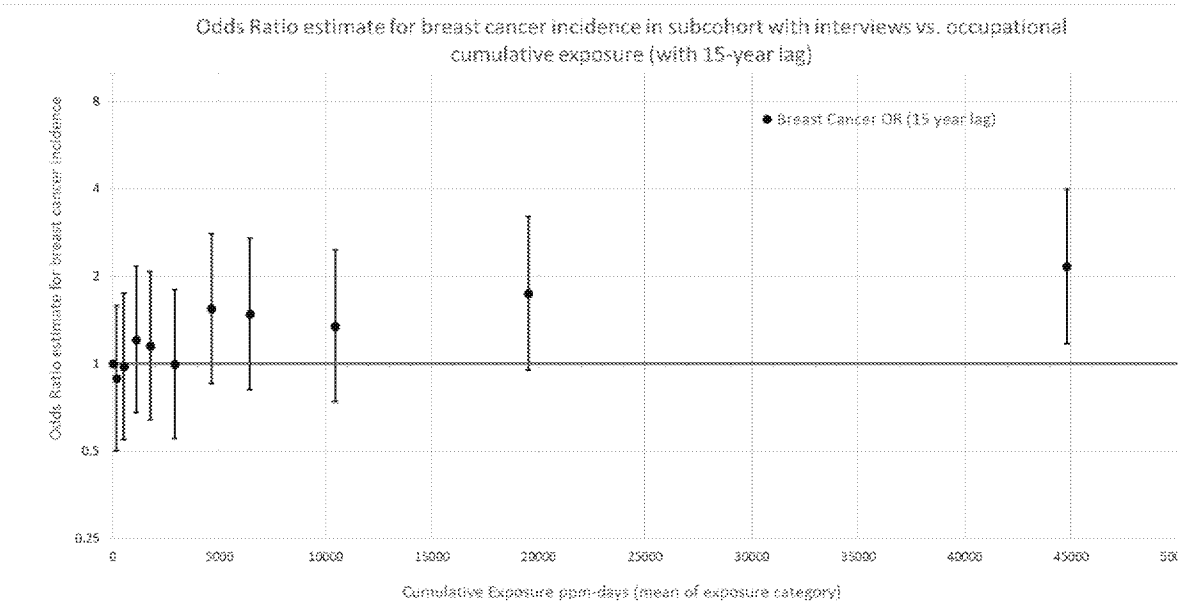
Data from IRIS (2016) Table D-1 and D-3. ORs with confidence intervals (CI's) are not consistent with a supralinear exposure response model. Medians of exposure category were not reported by IRIS. ORs with CIs that do not include 1 are statistically significant.

Figure 5 Odds Ratio for Lymphoid Cancer Mortality (15 year lag, both sexes) with log scale (Odds ratio and 95% confidence interval).



Data from IRIS (2016) Tables D-26 and D-28. ORs with CIs are not consistent with a supralinear exposure response model. ORs with CIs that do not include 1 are statistically significant.

Figure 6 Odds Ratio for Breast Cancer Incidence (15 year lag, females) with log scale (Odds ratio and 95% confidence interval).

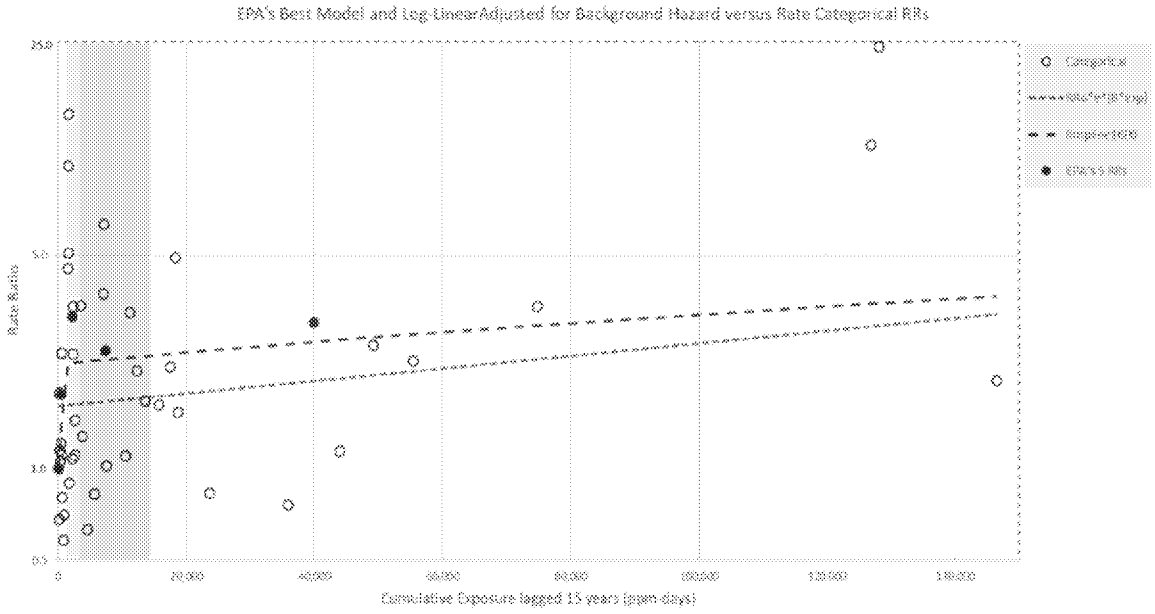


Data from IRIS (2016) Tables D-26 and D-28. ORs with CIs are not consistent with a supralinear exposure response model. ORs with CIs that do not include 1 are statistically significant.

More importantly, the IRIS figures (Figure 1 and 2) plot data points that represent grouped "categorical" data aggregated into quartiles or deciles instead of the actual individual cases (53 lymphoid and 233 breast cancer) modeled as shown in Figure 7. Although Figure 7 will also have very wide confidence intervals, it is far more representative of the exposure response pattern of the individual data that are modeled compared with Figures 1 and 2 that use only the 4 and 10 data points used by IRIS to evaluate visual fit.

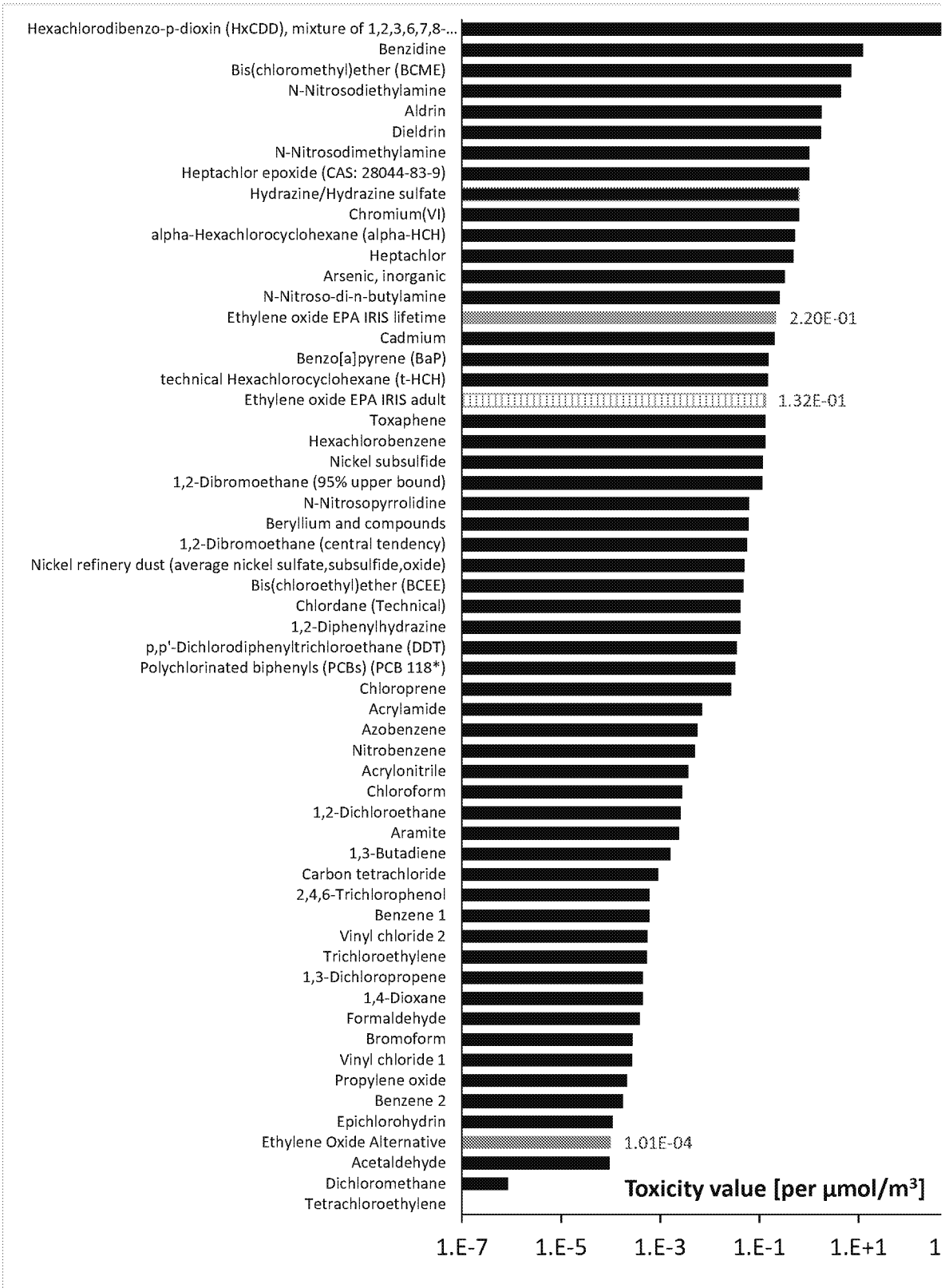
These data plots with few categorical data points mask the true exposure-response relationship as illustrated for lymphoid mortality in Figure 7 and described in greater detail by Valdez-Flores and Sielken (2013) for breast cancer mortality. Figure 7 also illustrates how the supralinear spline model (red dashed curve) and the standard CPH model (blue dashed curve) should be compared along the y-axis. From these observations, it is clear that selecting the model should not be based on the assumption that few summary odds ratios as point estimates describe the true underlying exposure-response relationship. The weight-of-evidence from the original epidemiology study do not support a supralinear slope or the consequent derivation of one of the highest UREs published by IRIS for inhalation cancer risks, including comparisons to unequivocal human carcinogens (Figure 8).

Figure 7 Lymphoid mortality comparing IRIS (2016) odds ratios for quartiles with more representative odds ratios (open circles) for individual cases for the purposes of comparing visual fit with the CPH and supralinear 2-piece spline model (TCEQ, 2019 Appendix 6 Figure 22; see text for discussion).



For an apples-to-apples comparison, the rate ratios are expressed as hazard rate divided by the non-parametric hazard rate at 0 cumulative exposures. This addresses the note in all the IRIS (2016) figures used for visual fit comparisons that "the different models have different implicitly estimated baseline risks; thus they are not strictly comparable to each other in terms of RR values (i.e. along the y-axis)"

Figure 8 IRIS inhalation URE in per µmole/m^3 for known or likely carcinogens



II. The ORD (2019) memo did not make a simple correction in statistical analysis that led to an incorrect conclusion that the 2-piece spline model has superior fit compared to the CPH model. Because the ORD memo—cited as a key basis for the proposed MON rule—is flawed, so is the dose-response analysis on which the proposed MON rule is based.

Based on the statistical analysis presented in IRIS (2016), ORD (2019) claims that the 2-piece spline model has superior fit compared to the CPH model. However, this conclusion is based on incorrect statistical fit calculations in the IRIS (2016) for the spline due to a simple error of not accounting for all the parameters. Prior to the ORD (2019) memo, TCEQ (2019) provided a detailed and complete evaluation of the statistical analysis presented in the IRIS (2016) appendices. TCEQ concluded that the selection of the 2-piece linear spline model and rejection of the CPH model is flawed by a simple error of not accounting for all three estimated parameters of the spline model[5].

The proposed MON indicates EPA reviewed the TCEQ (2019) assessment but appears to dismiss TCEQ's concern by claiming that the proposed TCEQ assessment had not been peer reviewed.

> TCEQ highlighted uncertainties in the URE arising from what it considered to be errors in the assumptions and calculations used to determine the best model fit of the data. TCEQ's concerns with the EPA's URE derivation have not been peer reviewed and the public comment period closed on September 26, 2019 (Fed Reg 2019 (Tues Dec 17); 84(242):69218).

However, the accounting for all the parameters in a model is not the type of claim that requires peer review to be valid, nor is documenting such a simple error typically considered by peer-reviewed scientific journals a matter worthy of publication and its associated peer-review process. TCEQ clearly demonstrated a simple error by the IRIS assessment due to incorrectly entering into the SAS statistical software the number of parameters estimated for the spline models.[6] TCEQ also provided the corrected AIC and p-

[5] The three parameters that were estimated by IRIS (2016) for all 2-piece linear spline models included those representing two slopes and the X-axis value of the "knot" or point of intersection that connects those two slopes

[6] "SAS statistical software used by IRIS required the user to ensure that a correct number of estimated parameters is entered into (or assumed by) that program when fitting a model to data. In the case of 2-piece spline model fits, the SAS program run for the IRIS assessment reflected only two estimated parameters, when in fact three parameters had been numerically optimized for this model (namely, the parameters representing two slopes and the X-axis value of the "knot" or point of intersection that connects those two slopes). This had the effect of making each resulting 2-piece spline model fit appear to be significantly superior to a corresponding simpler log-linear model fit, when in fact both models had statistically equally poor ability to fit the data (TCEQ 2019, pp. 124–129)."

values for the spline models that the ORD (2019) could have easily verified were correct and used instead of the incorrect IRIS (2016) values. Instead, ORD (2019) relied on the incorrect IRIS (2016) statistics to (in fact, erroneously) judge those fits for the 2-piece spline model to be significantly superior to corresponding fits obtained using the simpler more parsimonious CPH (i.e., "log-linear" risk with cumulative exposures) model.

This basic principle is clearly articulated in the National Research Council report entitled "Models in Environmental Regulatory Decision Making", which states that the strategy to pick the "best model" for regulatory decision making should be "*subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters versus having a parsimonious description*" (NRC, 2007, pp. 174). Importantly, there are no recognized exceptions to the penalty component of the balance incorporated into the AIC metric when applied in a valid procedure for model-selection (Burnham et al. 2002). This general principle is well recognized also to apply specifically to including the estimated "knot" or inflection point from 2-piece linear spline models (Berman et al. 1996, Li et al. 2011; Fearnhead et al. 2019, Gkioulekas et al. 2018, Rodríguez-Domínguez et al. 2018 Molinari et al. 2001). The ORD (2019) memo ignores these well-recognized principles and as a result eliminates the CPH model from consideration in the proposed MON RTR.

We highlight additional important points not previously presented in our comments on the HCl RTR:

- IRIS (2016 Appendix D.3.2. at p D-38) quoted the EPA SAB in justifying the statistical treatment in relation to the knot: "The knot is preselected and is not considered a parameter in these analyses, consistent with SAB's concept of parsimony [footnote 14: "in some setting the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example" [page 12 of SAB (2015)]".

  However, prior to fitting its two-piece spline model, EPA did not simply "fix" or "select" the position of the knot in that model "rather than estimating" its position, as specified by the SAB. Instead, IRIS tested 20 alternative knots for breast cancer and 70 knots for lymphoid mortality, and then among these, selected knot values that maximized the likelihood of data fit to a corresponding 2-piece spline model. This is not what EPA SAB intended when they suggested that the knot could be "pre-selected" prior to spline-model fitting. EPA SAB never indicated that IRIS could apply a procedure that violates basic statistical principles, as did the procedure ultimately applied by IRIS.

- In IRIS assessment Appendix D (at p. D-13), Dr. Steenland provided statistics taking into account the knot as a parameter for breast cancer to show this had no substantial effect in that analysis, but a similar examination was not presented in the case of lymphoid cancer. In other words, there was clear acknowledgement and recognition expressed in the IRIS assessment that each knot value that was used to obtain a final spline-model fit is appropriately interpreted as an estimated parameter. Thus, IRIS should have reported the p-values and AIC taking into account the knot as a parameter for breast and lymphoid cancers in the summary tables of the main report for greater transparency.

- TCEQ (2019) corrected the AIC and p-values reported by IRIS (2016) which are 464.5 and 0.14, respectively, for the IRIS selected 2-piece spline. The IRIS (2016) corresponding values for the CPH model are p=0.22 and AIC=464.4. These values are based on IRIS (2015) approaches. Thus, neither the 2-piece spline model nor the CPH model are statistically significant, and the AIC values are similar. Based on statistics alone, the CPH model fits the data similarly to the supralinear 2-piece spline slope, but has the advantage of parsimony (simpler model) and biological relevance. In addition, the CPH model more accurately predicts the observed lymphoid mortalities in the NIOSH study compared to the IRIS (2016) selected 2-piece spline model.

In conclusion, the MON rule is flawed because it depends on the ORD (2019) dose-response analysis, which fails to address and correct the specific, valid statistical considerations described above and in TCEQ (2019; at pp. 48-49). When corrected, the CPH model should be selected based on statistics alone. This results in a URE which is 3-orders of magnitude lower than that derived by IRIS (2016) based on the 2-piece spline model. The proposed MON (2019) amendment and the ORD (2019) sensitivity analysis should be corrected to include the CPH model as a valid model.

III. The ORD (2019) sensitivity analysis does not consider biological plausibility and consistency based on the results of the epidemiological studies. The overall weak findings suggest a shallow and not a steep exposure response at low exposures, and do not support derivation of one of the highest inhalation URE's.

The ORD (2019) sensitivity analysis focuses solely on statistical and visual fit considerations. In selecting a model for risk assessment, it is important to consider models that are consistent with the epidemiological data. It is important to keep into perspective

that the relevant epidemiology, despite the large number of human studies published over a forty-year period, indicates that there is only limited evidence of carcinogenicity (IARC 2012; see also ACC comments on the proposed HCl RTR).

While interest has centered on leukemia, other blood related malignancies, and recently breast cancer: (1) there are numerous inconsistencies across the studies, (2) elevated risks above background are found in isolated studies and the effect size is of small magnitude, and (3) there is an absence of a clear exposure-response relation for any specific cancer type (see ACC comments on the proposed HCl RTR). In a recent systematic literature review and meta-analysis, Marsh et al. (2019) concluded that the most informative epidemiology studies, which were published in the 2000s and 2010s, do not support the conclusion that exposure to EO is associated with an increased risk of lymphohematopoietic cancer or breast cancer. This weight-of-evidence is important to consider in selecting the model because there is no epidemiological evidence that EO is a highly potent human carcinogen.

The epidemiological evidence from the critical NIOSH cohort studies selected by IRIS neither supports the IRIS selection of a supralinear model nor the implication that EO is an extremely potent inhalation carcinogen. Our comments on the HCl RTR included a weight of evidence analysis of the lymphohematopoietic cancers that show that the overall evidence for an association with EO is weak and only seen at the highest exposure levels. In the NIOSH cohort, the graphs of the categorical odds ratio data in Section II of these comments reveal that when the confidence intervals are considered, there is no supra-linear spline pattern.

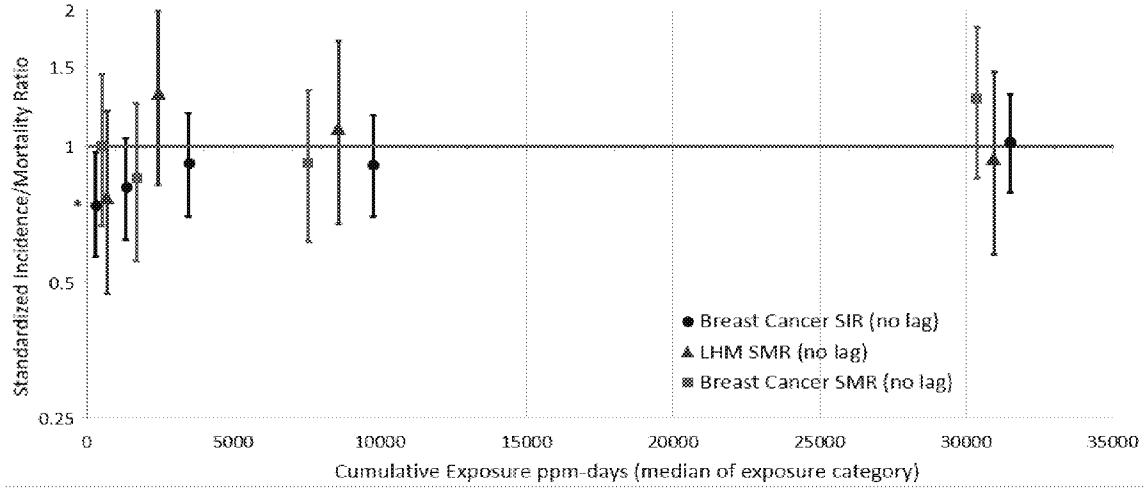
Steenland et al. (2003, 2004) also calculated standardized mortality ratios (SMRs) for lymphohematopoietic cancer mortality and standardized incidence ratios (SIRs) for breast cancer by categories of exposure (i.e. quartiles, quintiles and deciles) for 10-year lag. This type of analysis compares disease incidence or mortality in the exposed population against an external referent group. These SMRs and SIRs estimate excess risk for each category compared to the general population (e.g. life-table analysis for mortality analogous to the life-table analysis IRIS used).[7] There were no statistically significant SIRs or SMRs for breast cancer incidence and lymphohematopoietic cancer mortality (Steenland et al. 2003, 2004). The authors conclude "there was little evidence of cancer excesses" in the mortality data for all cancers examined and no excess of breast cancer in the whole cohort with a non-significant increase in the top quintile of cumulative exposures. These data are not indicative

[7] The results of the internal exposure-response analyses in the NIOSH cohort together with an actuarial program (life-table analysis) were used for predicting the extra risks of lymphoid cancer mortality (IRIS, 2016 p 4-9)

of a highly potent human carcinogen at lower cumulative exposures that the IRIS (2016) URE suggests.

At lower exposures (<647 ppm-days) there is a significant risk deficit (SIRs <1) for breast cancer incidence (Figure 9, black circle). With lag periods included, there are non-significant risk deficits (SIRs and SMRs <1) for both breast cancer incidence below 2,026 ppm days and lymphohematopoietic cancer mortality below 1,199 ppm-days (Figure 10). One possible explanation is that there is a healthy worker effect (HWE) in this cohort. However, the epidemiologic literature has shown that HWE is predominately related to populations with shorter follow up and non-cancer causes (Monson 1986; Fox and Collier 1976). Kirkeleit et al. (2013) report no statistically significant healthy worker effect for breast cancer and lymphoid and hematopoietic tissue cancers. Steenland et al. (2004) concluded that "the healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons". These data for breast and lymphoid cancers are not consistent with an extremely potent inhalation human carcinogen, especially at lower exposure levels. In fact, the SIR pattern appears to have a sublinear dose-response at the lower exposures.

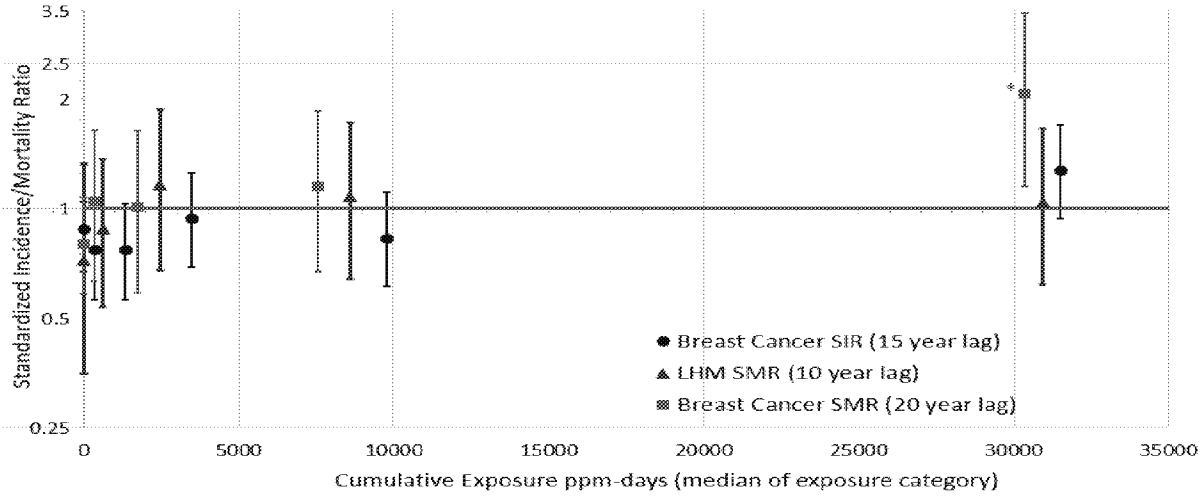
Figure 9 Steenland et al (2003, 2004) lymphohematopoietic cancer mortality, breast cancer mortality, and breast cancer incidence (no lag period).



The breast cancer SIRs (black circles) and 95% confidence intervals (bars), lymphohematopoietic cancer SMRs (red triangles), and breast cancer SMRs (blue square) by increasing EO ppm-days quintiles (>0 to 647, 647 to 2,026, 2,026 to 4919, 4,919 to 14,620, >14,620 ppm-days), quartiles (>0 to 1,199, 1,200 to 3,679, 3,680 to 13,499, >=13,500 ppm-days), and quartiles (>0 to 646, 647 to 2,779, 2,780 to 12,321, >=12,322 ppm-days), respectively. SIR and 95% confidence interval data come from Table 3 in Steenland et al. 2003, and SMR data comes from Tables 3 and 5 from Steenland et al. 2004. SMR 95% confidence intervals were calculated by first deriving the expected values from the numbers provide in Table 3 (Expected = Observed/SMR) and then using the Mid-P exact test [Miettinen's (1974d) modification, as described in Rothman and Boice (1979).

Steenland et al. (2003) indicate that the SIRs are underestimated because breast cancer incidence in the whole cohort was under-ascertained, due to an incomplete response from workers and lack of complete coverage by state cancer registries. This problem of incomplete ascertainment alone is sufficient reason to exclude these data for any quantitative cancer risk assessment because it introduces uncertainty and potential bias in the analysis for not only analysis based on external referent populations but also when internal nested case-controls are used followed by life-table analysis to estimate excess risk. Steenland et al. (2003) concluded that "there are possible biases due to patterns of non-response and cancer ascertainment which introduce additional uncertainties in the findings," and concluded that the epidemiological evidence was only suggestive for breast cancer.

Figure 10 Steenland et al (2003, 2004) lymphohematopoietic cancer mortality, breast cancer mortality, and breast cancer incidence with lag periods included



The breast cancer SIRs (black circles) and 95% confidence intervals (bars) with 15 year lag, lympho-hematopoietic cancer SMRs (red triangles) with 10 year lag, and breast cancer SMRs (blue square) with 20 year lag by increasing EO ppm-days quintiles (0 (lagged out), >0 to 647, 647 to 2,026, 2,026 to 4,919, 4,919 to 14,620, >14,620 ppm-days), quartiles (0 (lagged out), >0 to 1,199, 1,200 to 3,679, 3,680 to 13,499, >=13,500 ppm-days), and quartiles (0 (lagged out), >0 to 646, 647 to 2,779, 2,780 to 1,2321, >=12,322 ppm-days), respectively. SIR and 95% confidence interval data comes from Table 3 in Steenland et al. 2003, and SMR data comes from Tables 3 and 5 from Steenland et al. 2004. SMR 95% confidence intervals were calculated by first deriving the expected values from the numbers provide in Table 3 (Expected = Observed/SMR) and then using the *Mid-P exact test* [Miettinen's (1974d) modification, as described in Rothman and Boice (1979).

In conclusion, the IRIS (2016) and ORD (2019) did not reality check the biological plausibility of the models (i.e. consistency of EO cancer predicted by the models) with the actual epidemiological data. When this is done, the weight of evidence based on the epidemiological data is far more consistent with the CPH rather than a steep 2-piece spline slope.

IV. Lymphoid morality in humans is an appropriate health outcome for risk assessment, as is, without transformation to incidence. The overall weak findings of the lymphoid mortality data suggest a shallow and not a steep exposure response at low exposures. These data are not consistent with the IRIS derivation of one of the highest inhalation URE's.

In the NIOSH cohort, there was little evidence of cancer excesses by levels of cumulative exposure for the EO exposed workers versus the general population (Steenland et al. 2003, 2004). A large number of models were considered in their exposure-response analyses and only some sub-analysis showed significance including those using log transformation of cumulative exposure, which IRIS (2016) correctly excluded as biologically implausible. Of the models using cumulative exposures, the strongest trend was seen in male lymphoid mortality. As described in detail in the next section, breast cancer incidence is not an appropriate endpoint based on the weight-of-evidence and quality issues. Therefore, of the critical endpoints selected by IRIS, male lymphoid mortality is the most appropriate endpoint for risk assessment, protective of effects in females who showed no sensitivity.

The cancer risk assessment should be based on lymphoid mortality as the appropriate health outcome without further manipulation to estimate extra risk for lymphoid incidence. The NIOSH study did not collect lymphoid incidence data. IRIS converted lymphoid mortality to lymphoid incidence based on unsupported assumptions that have been shown to introduce error and bias into the analysis (Sielken and Valdez-Flores 2009; Teta et al. 2004). The original data collected by NIOSH should be used without further manipulation that could lead to incorrect characterization of the exposure-response relationship.

It is important to keep into perspective that the relevant epidemiology, despite the large number of studies published over a forty-year period, provide insufficient support based on limited evidence of carcinogenicity (IARC 2012). While interest has centered on leukemia, other blood related malignancies, and recently breast cancer: (1) there are numerous inconsistencies across the studies, (2) elevated risks above background are found in isolated studies and the effect size is of small magnitude, and (3) there is an absence of a clear exposure-response relation for any specific cancer type. In a recent systematic literature review and meta-analysis, Marsh et al. (2019) concluded that the most informative epidemiology studies, which were published in the 2000s and 2010s, do not support the conclusion that exposure to EO is associated with an increased risk of lymphohematopoietic cancer or breast cancer. This weight-of-evidence is important to consider in selecting the model because there is no epidemiological evidence to support the IRIS derivation of a URE that suggests EO is a highly potent inhalation human carcinogen.

V. Although useful for consideration of the overall weight-of evidence, breast cancer should not be considered a critical cancer endpoint for quantitative risk assessment purposes based on the weak findings in Steenland et al. (2003, 2004) and weight-of-evidence in the epidemiological literature. The breast cancer incidence data should not be used for quantitative risk assessment purposes based on substantial under-ascertainment of cases reported by Steenland et al (2003) compounded by risk deficits in the lower exposures.

The key reasons why breast cancer should not be considered a critical cancer endpoint for EO are as follows:

1) Neither the NIOSH breast cancer incidence study (Steenland et al. 2003) nor the NIOSH mortality study (Steenland et al. 2004) report an overall excess of breast cancer.
2) The findings are not robust in that they are seen with a certain lag and exposure metric that are not evident with numerous other exposure metrics, models, or lags.
3) The breast cancer incidence findings are at most suggestive, not only due to inconsistencies in the exposure-response, but also due to incomplete cancer ascertainment and the subsequent potential for bias.
4) This disease endpoint is only weakly supported by other epidemiology studies and is inconsistent with others.

The published epidemiology data do not support a supralinear exposure-response relationship for breast cancer. The limited positive findings in the published NIOSH incidence study is seen in the highest exposure category only, not in the lowest or lower levels (Steenland et al. 2003). As described in detail in the previous section, IRIS incorrectly chose a supralinear model based on visual appearance of a limited number of categorical data points. This model is inconsistent with the fundamental NIOSH data published by Steenland et al. (2003, 2004).

For purposes of hazard assessment and choice of a health endpoint, it is useful to examine all relevant EO studies, even those inadequate for exposure-response analyses. There is no pattern of increase across these six studies and the overall number of observed breast cancers do not exceed expectation, whether based on mortality (113 observed, 116 expected) or incidence data (372 observed, 425 expected) (see Table 2). In a recent EO meta-analysis based on effect measures from 5 studies, Marsh et al. also failed to find increased risk for breast cancer among sterilization workers (meta-RR=0.97; 95%CI 0.81-1.18) (Marsh et al. 2019). The most informative cohort and largest contributor reported results very close to expectation (mortality, SMR =0.99) or a significant deficit (incidence SIR=0.87) due to case under ascertainment (Steenland et al. 2004 and 2003, respectively).

The findings from EO epidemiology conflict with the IRIS risk values which imply EO is a very potent carcinogen.

Table 1 Female Breast Cancer: Overall Observed less than Expected

Study	Observed	Expected	Obs./Exp.
Coggon et al. 2004	11	13.1	0.84
Steenland et al. 2004	102	103	0.99
Steenland et al. 2003	319	367	0.87*
Mikoczy et al. 2011	41	50.9	0.81
Norman et al. 1995	12	7.00	1.72
Hogstedt et al. 1986	0	---	---
Summary (incident cases only)	372	425	0.88*
Summary (mortality cases only)	113	116	0.97

*Statistically significant but of less interest due to under ascertainment of cases

Although both the NIOSH breast cancer mortality and the breast cancer incidence studies found no increased breast cancer rates overall, they reported some evidence of a trend and increased rates in the highest exposure group for certain forms of exposure modeling but not for others, in the wide variety of statistical analyses conducted (continuous, categorical, cumulative exposure, log of exposure, duration of exposure, lag, no lag, etc.). The authors concluded conservatively, "Our data suggest that ETO is associated with breast cancer…" These suggestive findings were not robust, which would be expected with a potent carcinogen.

The IRIS breast cancer incidence analysis relied on incomplete data from the subpopulation of the NIOSH cohort that was interviewed, which required both locating subjects and identifying those diagnosed with breast cancer. Of the 7,576 women in the NIOSH cohort, only 5,139 (68%) were included in the interview portion of the study. The percent non-response was of concern, according to the authors. The majority of these, 22%, could not be located and therefore any breast cancer diagnosis would have been missed. Cases lost to follow up are more likely to be shorter term (i.e. lower cumulative exposure) employees. Those who work longer (i.e., higher cumulative exposures) stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview. Shorter duration workers with lower exposures are more likely to leave the area and not be

captured in the overall analyses and less likely to be interviewed. Their diagnoses get missed, creating a possible biased, positive exposure-response relationship.

The question then is whether the interviewed population is representative in terms of exposure-response patterns of the fully ascertained cases in the total population. This has been shown not to be the case in some studies (Haneuse, 2016), i.e., participant data alone does not accurately represent the intended study population (participants and non-participants collectively). Kristman et al. (2004) reported serious bias, even in the case of low loss to follow up, when loss to follow up is not random. Steenland et al. (2003) recognized this possibility and stated they were unable to fully address it.

A simple approach was not employed, i.e., to examine in the full population whether the proportion not interviewed was related to level of exposure. If more cases were missed among those with lower cumulative exposures (shorter term employees), then the data would be biased toward seeing a positive slope and/or elevated risk in the higher exposure groups, as reported by Steenland et al (2003). The lower exposure group(s) would have a deficit of cases. The possibility of such a bias is strengthened by the finding in this publication of a stronger relationship with duration of employment than with cumulative exposure.

Due to the statistically significant deficit of 0.82 in the overall SIR analysis, Steenland et al. (2003) conducted internal analyses of this exposed population, i.e., workers to workers. Steenland et al. (2003) states that there is complete ascertainment of diagnoses in the interviewed group, however, this does not correct for possible selection bias in that the exposures of these interviewed cases may not be representative of the full cohort due to cases who could not be located. The internal analysis approach assumes that the under ascertainment of breast cancer cases in the interviewed subgroup is unrelated to level of exposure, which is questionable as discussed above.

Such internal analyses are also conducted when there are concerns about the HWE. However, the epidemiologic literature has shown that HWE is predominately related to shorter follow up and non-cancer causes. (Monson 1986; Fox and Collier 1976). The NIOSH cohort has been followed an average of 25 years. This issue was examined by Gridley et al. (1999) specifically for cancer incidence among Swedish women. The results showed no HWE for breast cancer. Kirkeleit et al. (2013) also report no statistically significant healthy worker effect for breast cancer.

The substantial deficit of cases for breast cancer incidence could have led to non-random cases lost to follow up for the subcohort with interviews. In general, shorter term workers are more difficult to find for interviews, and this can introduce bias in the analysis. This

together with the unavailability of the breast cancer incidence data to other researchers raises quality issues that indicate the data are inappropriate for exposure-response modeling for regulatory cancer risk assessment purposes.

The choice of a supralinear 2-spline model to calculate the URE for breast cancer incidence was heavily weighted by a visual examination of five odds ratios (grouping of data into five exposure categories) from the Steenland et al. (2004) incidence data. The odds ratio in the highest exposure category was significantly elevated (1.87, 95%CI=1.12-3.10). This corresponds to an open-ended cumulative exposure category (greater than 14,620 ppm-days). The remaining odds ratios starting with the lagged-out reference group were 1.00 1.06, 0.99, 1.24, 1.42. Although few in number, these results are clearly not suggestive of supralinearity. The authors observed that when categories of exposure were expanded from five to ten, a different pattern or lack thereof emerged from a decile breakdown (0.88, 1.35, 1.00, 1.00, 1.33, 1.22, 1.40, **1.03**, 1.68, 1.82; bold added to emphasize non-monotonic exposure response).

Using categorical, i.e., grouped data to identify an exposure-response model can be misleading, and the pattern can change as the number of categories are expanded (Valdez-Flores and Sielken, 2013). The odds ratios from the Steenland et al. (2003) breast cancer incidence study appear far from supralinear, as one increases the number of categories examined, as was also illustrated by Valdez-Flores and Sielken (2013). As these authors point out, exposure-response models are best fit with individual rather than summarized data, as recommended by the SAB and followed by IRIS in their actual modeling. Unfortunately, however, IRIS picked their model *a priori* based on limited categorical data without consideration of CIs.

The exposure-response modeling challenges in the NIOSH publication (and later experienced by IRIS) could be anticipated, given the authors' statement of uncertainty with respect to breast cancer incidence, "The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure" (Steenland et al. 2003). The other studies that examined breast cancer among women exposed to EO also provide inconsistent results.

Norman et al. examined cancer incidence among 1,132 male and female workers in a medical sterilant plant under active medical surveillance (Norman et al. 1995). The period of potential EO exposure was 1974-1980 and follow up was through 1987. There were 12 breast cancers found among the total of 28 identified cancer cases. Time from first exposure to diagnosis was 11 years or less for each of the 12 cases. These cases would all fall in the NIOSH lagged out group which had a 15-year lag and would therefore be part of the referent group (Steenland et al. 2003). Two of the cases worked at the facility for less

than 1 month. Because this was not a well-defined cohort with follow up, the authors used various assumptions and methodologies to calculate person years at risk that yielded a range of SIRs from a statistically significant 2.6 (95% CI: 1.3-5.0) to a non-significant 1.7 (95% CI: 1.0-3.0).

The more recent study by Mikoczy et al. (2011) has been incorrectly cited as supportive of a supralinear association with breast cancer, despite an overall deficit of breast cancer (SIR= 0.81), with or without consideration of a latency period. However, the two higher cumulative exposure groups had statistically significant elevated rates of breast cancer in an *internal* Poisson analysis, due to a substantial and statistically significant deficit of breast cancer in the low dose reference group. This deficit is not explained by the HWE, which is primarily related to non-cancer causes and declines with length of follow up.

This issue was examined by Gridley et al. (1999) specifically for cancer incidence among Swedish women. The results showed no HWE for breast cancer. There are clearly advantages to comparing workers to workers in epidemiology studies to overcome possible biases in external comparisons to the general population. However, there may also be disadvantages to using an internal comparison group that may not be recognized. One danger is selecting a referent group that has an unusual deficit of the disease of interest that creates an artifact of an excess as is illustrated in this study. The IRIS report quantitatively demonstrated the inconsistency of the excesses reported at very low exposures in this population with excesses at only higher exposures in the NIOSH study.

Eight hospitals with EO sterilizer units in England provided 1012 women for a cohort study initially conducted by Gardner et al. (1989) then updated by Coggon et al. (2004). No industrial hygiene data were available before 1977, but exposures were less than 5 ppm after 1977. Peaks of several hundred ppm were known to have occurred from loading and unloading of sterilizers in the hospitals. The authors felt earlier exposures would have been higher and both settings reported peak exposures above the odor threshold (700ppm). Dates of first EO exposure varied from 1962 to 1972 for the hospitals. This study reported no increase in breast cancer (11 deaths observed versus 13.1 expected).

After repeated attempts by the Panel, NIOSH has refused to share the incidence data from the NIOSH study. This prevents other researchers from evaluating the bias potential of under ascertainment of breast cancer cases, try alternate or improved methodologies and models, and verify the NIOSH incidence study and the IRIS exposure-response results, as has been done with lymphoid mortality data.

The authors of the NIOSH study noted that the mean number of ppm-years for the cohort (26.9) is much greater than the median (5.6), indicating a skewed distribution suggesting

that there may be a number of subjects with very high cumulative exposures in the highest exposure category. If so, drawing conclusions based on summarized data in the highest exposure category, with the cut-point of 12,322+, could be misleading. Having access to the NIOSH breast cancer mortality data some years ago, we were able to conduct a sensitivity analysis related to this choice of the highest exposure cut point (see Appendix A).

Our results with mortality data were consistent with observation in the incidence study that breast cancer excess risks showed an "inconsistent or non-monotonic risk with increasing exposure" (Valdez-Flores et al. 2010; Steenland et al. 2003). The consequence of this pattern (or lack thereof) is that it is not possible to identify a definitive cut-off above which excess risk appears. In the analyses relied upon by Steenland et al. (2003) in the mortality study (cumulative exposure and 20 yr. lag), cumulative exposure above the 70% and 75% as the highest exposure category produce statistically significant increases. But if higher cut-offs were chosen, (80%, 85%, 90%, 95%), the SMRs decreased and none are statistically significant (Appendix A).

In conclusion, s*uggestive* findings related to breast cancer, with 1) no overall excess, 2) uncertainties in important areas of exposure-response 2) possible bias associated with case under-ascertainment and 3) lack of consistency with other studies, should not become the basis for a URE.

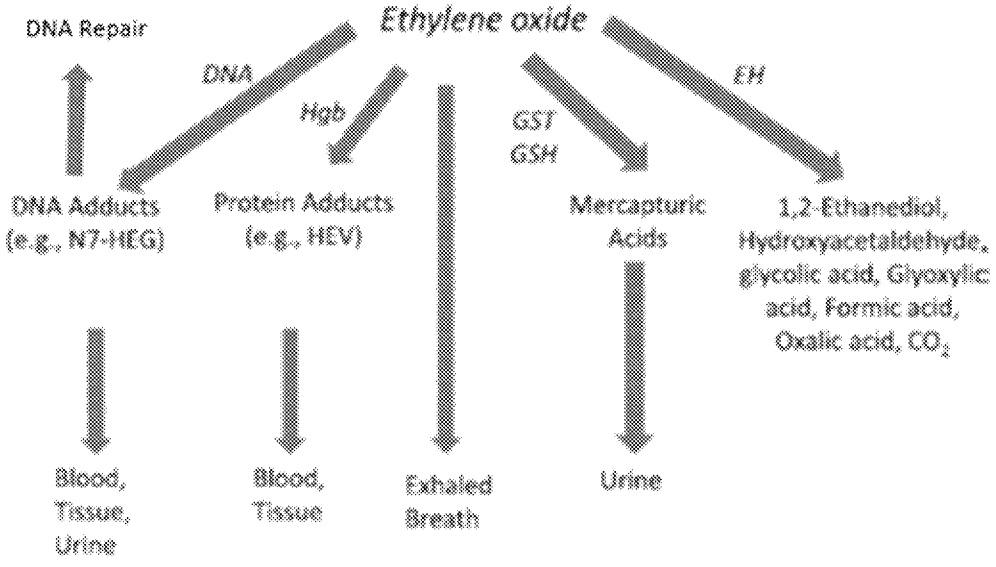
VI. IRIS (2016) did not consider the biological plausibility of models based on the biological mode of action and toxicological evidence, which support a shallow linear exposure-response at lower exposures. IRIS has not offered any biologically plausible mode of action analysis accounting for a supralinear dose-response of EO in the low-exposure range. In contrast, considerable experimental mode of action data consistently indicate it is highly implausible that EO operates by supralinear exposure response in the exposure region estimated by IRIS as increasing cancer risks.

A. The Hypothesized Mode of Action and Toxicokinetic Data Indicate a Low-Dose Supralinear Exposure-Response Model Is Biologically Implausible

EO is a direct-acting alkylating agent that forms adducts with hemoglobin, DNA and other cellular macromolecules.

The long-held hypothesized MOA of EO is attributable to the initial key molecular initiating event of direct reactivity with DNA, (see Figure 11).

Figure 11 Disposition and Detoxification of Inhaled EO. DNA= deoxyribonucleic acid; Hgb = hemoglobin; EH = epoxide hydrolase; GSH= glutathione; GST = glutathione-S-transferase; N7-HEG = N7-hydroxyethyl guanine; HEV = N-2-hydroxyethyl valine.

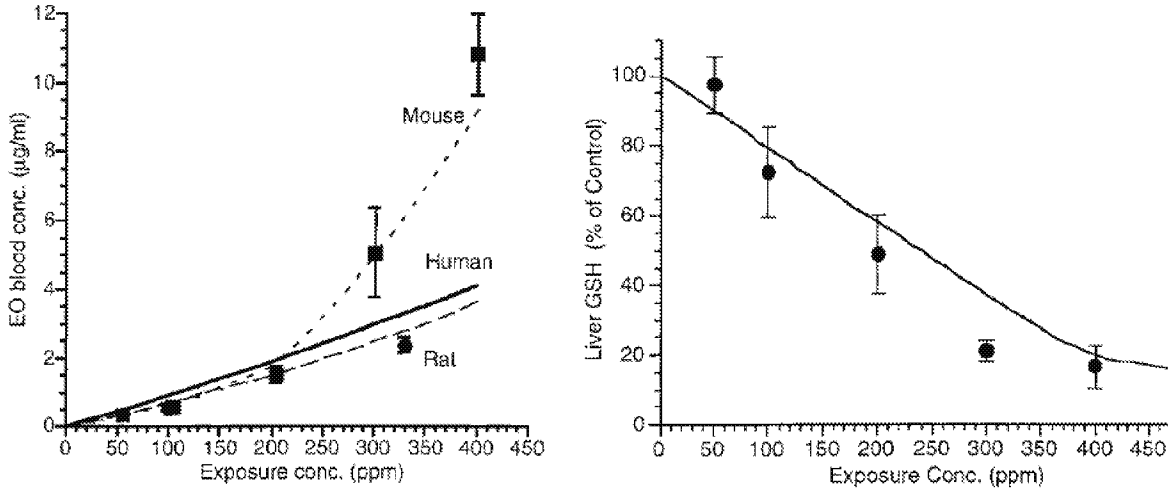


Modified from Kirman & Hays, Reg Toxicol Pharmacol 91: 165-172, 2017

As described previously in ACC comments on the proposed HCl RTR, the metabolic pathways describing the overall disposition of EO are well characterized, i.e., detoxification by direct or enzymatically-mediated conjugation with glutathione and epoxide hydrolase conversion to non-reactive metabolites. In addition, DNA adducts induced by EO are rapidly spontaneously depurinated and/or undergo enzymatic DNA repair. None of these pathways are expected to operate by a supralinear exposure-response under conditions of low-dose exposure (Filser and Klein, 2018).

In Figure 12, Fennell and Brown (2001) have shown that EO blood concentrations in mice, rats and humans increased linearly with exposures between 50 and 200 ppm. Blood EO increased disproportionately only in mice at exposures exceeding 200 ppm, which was due to substantial depletion of glutathione (GSH) limiting the overall GSH conjugation capacity (GSH, Figure 12).

Figure 11 Toxicokinetics of ETO from Fennell and Brown (2001).



Left panel: Dose-dependent toxicokinetics of ETO in mice, rats and humans.
Right panel: Dose-dependent depletion of liver GSH in mice.

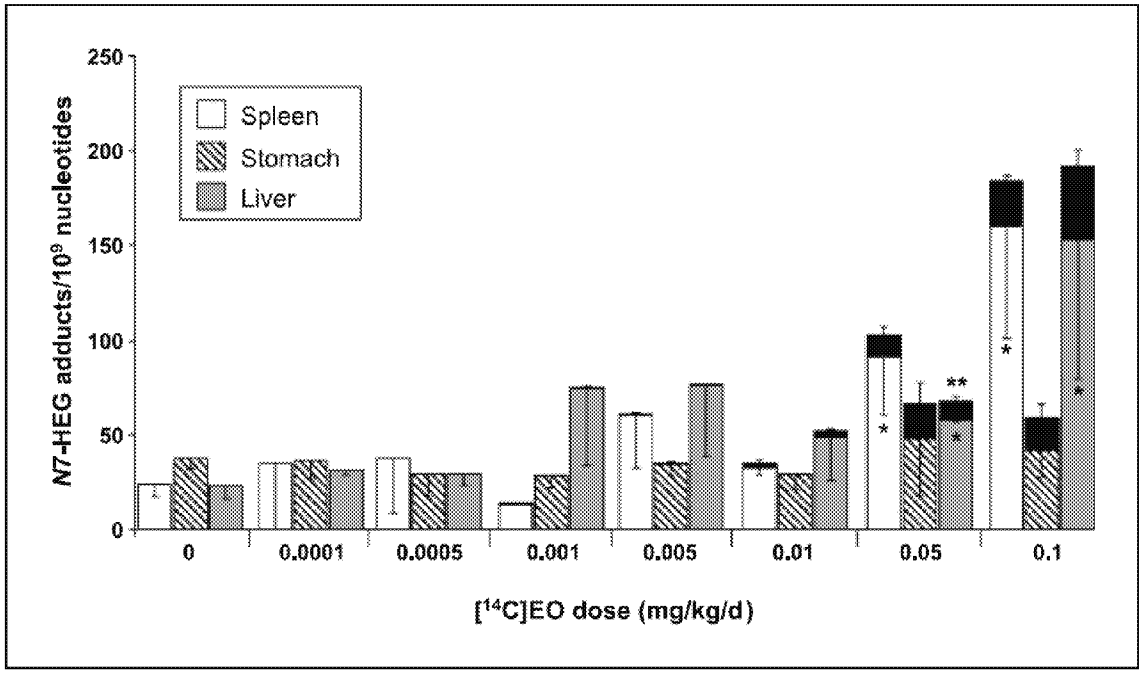
B. Dosimetry of EO DNA adduct formation in rats exposed to EO does not support a low-dose supralinear spline slope

The key molecular initiating event in the mode of action for EO has been hypothesized to be EO DNA adduct formation. In comments ACC submitted on the proposed HCl RTR, we highlighted the dose response of formation of the predominate DNA adduct (N7-(2-hydroxyethyl)guanine; N7HEG) formation in rats associated with a wide range of EO exposures (Marsden et al. 2009).

These data indicate that EO did not exhibit any evidence of a supralinear dose-response in the formation of DNA adducts over the range of lower doses evaluated in this study (Figure 13). Importantly, the total combined endogenous plus exogenous DNA adduct burden was statistically significantly increased only in liver at the second highest 0.05 mg/kg/day dose. Thus, these data indicate that if total DNA adducts were measured by a highly sensitive non-radiolabeled method over a wide range of exogenous EO treatments, such sensitive analyses would not be able to statistically differentiate DNA adducts between controls and treated rats until a dose of 0.05 mg/kg/day. These data are consistent with a sublinear, and more conservatively, a linear exposure response.

In addition, the lowest dose tested in the rat DNA adduct study, 0.0001 mg/kg/day is approximately 4 orders of magnitude greater than an equivalent EO systemic dose received by humans inhaling 0.1 ppt EO[8]. These data indicate it is highly unlikely that a 0.1 ppt EO human exposure results in increased tissue DNA adducts until EO exposures far higher than 0.1 ppt are experienced, and provide further MoA evidence that EO is not capable of increasing cancer incidence in the low-dose exposure region predicted by the IRIS supralinear spline dose response model.

Figure 12 Contribution of endogenously and exogenously derived N7-HEG to the total adduct level in tissues of ^{14}C EO-treated rats from Figure 2 of Marsden et al. (2009)



[8] This estimation is based on the following assumptions: 0.1 ppt = 0.18 ng/m^3; humans inhale 20 m^3 air per 24 hr with a 75% respiratory retention (Brugnone et al., 1985), 70 kg body weight.

C. Integration of the tumorigenicity findings from the ethylene and EO rat ethylene and EO carcinogenicity studies also supports a conclusion that the supralinear spline exposure-response model is biologically implausible.

The lack of biological plausibility of the supralinear spline exposure-response is further informed by integration of carcinogenicity findings from the F344 rat carcinogenicity bioassays of ethylene and EO. Because ethylene is metabolized to EO, data from the ethylene bioassay can be integrated with that of the rat EO carcinogenicity study to further inform the shape of the EO rat carcinogenicity exposure response.

Ethylene has been evaluated for F344 rat carcinogenicity following a 2 yr inhalation exposure of 300, 1000, and 3,000 ppm (Hamm et al. 1984), and was not carcinogenic at the highest tested exposure. Filser and Klein (2018) used PBPK modeling to estimate that 3,000 or 1000 ppm ethylene exposures in rats (6 hr/day, 5 days/week) were equivalent to 5.52 or 5.26 ppm EO, respectively, in rats. A 40 ppm ethylene exposure was equivalent to 1.26 ppm EO. Importantly, these results were based on modeling of ethylene exposures that resulted in the same levels of HEV adducts or DNA adducts as those produced by equivalent 6 hr/day, 5 days/week EO exposures. Thus, ethylene was not carcinogenic in rats at a maximum EO equivalent exposure of 5.52 ppm. Overall, the combined ethylene and EO rat carcinogencity data are inconsistent with the hypothesis that EO operates by supralinear exposure-response in the low exposure postulated from the epidemiological exposure-response analysis.

Human background endogenous exposure to EO has been estimated by hemoglobin HEV adduct analyses as equivalent to 1,900 ± 1,300 ppt of exogenous EO (Kirman and Hays, 2017). Acknowledging this high background endogenous exposure, EPA IRIS (2016) has stated that "it is *highly plausible* that the dose-response relationship *over the endogenous range* is sublinear" [emphasis added]. The basis for this conclusion was the knowledge that EO molecular and tissue injury is moderated at low EO exposures by a multiplicity of overlapping biological defenses including primary detoxification by GSH transferase and epoxide hydrolase and secondary intervention of DNA repair (Figure 11).

These data further indicate that it is highly biologically implausible that the contribution of an additional 0.1 ppt exogenous EO to, e.g., an existing 1,900 ppt background endogenous EO exposure, would result in a sudden and biologically unexplained shift to a supralinear dose response and mode of action. This is particularly so considering that such an additional minute exogenous EO exposure is also a very small fraction of even the reasonable variability range of normal human endogenous background EO exposures (1,300 ppt).

In conclusion, as a reactive chemical capable of alkylating DNA, but whose toxicity is modulated by DNA repair and epoxide clearance mechanisms (GSH transferases, epoxide hydrolase) common to rodents and humans, there is no mechanistic rationale to suggest that EO operates by a supralinear exposure response in the low exposure region projected by IRIS as increasing cancer risks. Indeed, this is also consistent with the observations that there was no excess risk when considering the weight of evidence for the epidemiological studies on EO and the relatively few statistical findings when considering the SIRs, SMRs, odds ratios for the breast cancer incidence and lymphoid mortality data from the Steenland et al. (2003, 2004) studies.

D. The IRIS cancer potency estimate for EO is inconsistent with its weak genotoxic potency.

Several investigations addressed the genotoxicity of EO using *in vitro* and *in vivo* test systems. Given that EO is a direct acting DNA-reactive molecule, it is not surprising that positive results were observed in the majority of these studies. However, EO is a relatively weak mutagen, but the large number of positive studies led to the misunderstanding that it is a potent mutagen (Waters et al. 1999).

A key study indicating supporting the weak mutagenicity of EO comes from the subchronic inhalation study of Manjanatha et al. (2017). These authors investigated the dose-response and temporality for EO-induced mutations at the *cII* locus in the lung tissue of transgenic Big Blue male B6C3F1 mice, a species/strain/sex/tissue where tumors were observed in the EO bioassay. Consistent with mode of action framework analysis objectives, the study design was based on the prediction that if EO-induced mutations were responsible for its tumorigenicity, it should induce mutagenicity in the tumor target tissue at a dose equal to or lower than the tumorigenic dose.

Furthermore, if EO is acting via a mutagenic MoA, the mutant frequency for a neutral gene like *cII* should increase at an early time point, and then continue to increase with continued exposure. Contrary to expectations that are consistent with a mutagenic MoA, no statistically significant increase in mutant frequency or mutational spectrum were observed following 4 weeks of EO exposure (which is considered to be adequate exposure duration for detecting chemically-induced mutations as per OECD test guideline 488), but a significant increase was observed only following 8 or 12 weeks of exposure and only at a concentration (200 ppm) twice the tumorigenic dose in the bioassay. Furthermore, there was no increase in the mutant frequency with exposure duration of 8 and 12 weeks. These data are not consistent with the modified Hill criteria for dose-response and temporality for a mutagenic MoA. This study also demonstrated EO to be weak mutagen with only a small

increase in mutant frequency over the background (< 3-fold) even at a concentration twice the tumorigenic dose.

Taken together, genotoxicity data support a conclusion that EO is a weak genotoxicant and implausibly associated with a supralinear exposure response at low exposure.

VII. The ACC alternative proposal for URE is conservative and has a dose-response form that is both biologically plausible and consistent with the observed data. The rationale for selection of the critical endpoint and point-of-departure are summarized.

Our comments support the conclusion that EPA should not use the EO IRIS Assessment's inhalation RSC of 0.1 ppt to calculate EO risk in its ongoing RTR rulemakings. A more reasonably conservative and scientifically supportable approach to an exposure response analysis is the approach developed by TCEQ (2017). This alternative approach yields 1/M RSC ranges of 240 – 500 ppt. The point-of-departure and URE values based on the CPH model for lymphoid mortality cases are conservative because extra risk was calculated despite no statistically significant slope in the exposure-response analyses.

The MON includes a range of possible values for cancer risk. We agree with considering a range of values including central estimates, but the ORD memo ignored a much more standard statistical model—a CPH model—that has comparable statistical and visual fit to the one selected by IRIS. More importantly, this model has greater biological plausibility fitting EPA SAB's selection criteria for models.

The EO Panel strongly disagrees with ORD's emphasis of visual fit based on a few categorical odds ratio data points which are not the data modeled. ORD ignored the CPH model based on misrepresentations of visual fit and incorrect statistics. We also disagree with including the linear regression of the categorical data which the SAB explicitly stated should not be used because they are not based on the individual data and the full data set should be included.

Our proposed alternative approach is based first on the weight-of-evidence from the epidemiological literature and the Steenland et al. (2003, 2004) papers for determining the critical endpoints, and then we apply the CPH model using the same lag period that IRIS (2016) selected.

As discussed previously, breast cancer incidence is not an appropriate endpoint for risk assessment purposes. The lymphoid mortality was considered by Steenland et al. (2004) to be the more robust finding, with males more sensitive than females. This effect in males,

and males and females combined, was modeled using the CPH model with cumulative EO exposure (ppm-days) treated as a continuous variable.

A 1/100,000 extra risk level was estimated consistent with EPA (2005) cancer risk assessment guidelines on selection of the PoD at the low end of the observable range of responses. When the standard Cox proportional hazard (log-linear) model is used for the NIOSH males-only 15-year lag data, all of the lymphoid mortalities with non-zero exposure occurred **below** the 1 in 100 PoD (Table 3). Therefore, 1 in 100 is not an appropriate PoD for "extrapolation" in the conventional sense.

A typical POD extrapolates from the edge of the observed range through the unobserved range of the data. Thus, for the NIOSH male only data, it is appropriate to use the model to extrapolate to 1 in 100,000, which is below the 50^{th} percentile of exposure where there is only one lymphoid mortality for subjects with non-zero exposure. IRIS (2016) used a 1% (1 in 100) extra risk for the PoD but did not provide evidence that this level would establish a PoD near the edge of the observed data range. The CPH model has the general form $\exp(\beta z)$ and is usually described as a sublinear model. However, it is notable that this model becomes linear at extra risk levels of 1/100,000 as concentration "z" approaches zero.

Table 3 Number of male lymphoid cases from Steenland et al. (2004) with concentrations below the EC(1/100) and EC (1/100,000)

	Male Lymphoid EC 1/100		Male Lymphoid EC 1/100,000[2]	
	0-LAG	15-Lag	0-Lag	15-Lag
EC (1/100,000) Env. Conc (ppm)	3.52	5.80	5.83E-03	9.67E-03
Equivalent[1] Occupational Exposure 70 years (ppm-days)	326,105.92	354,399.0[2]	453.4[2]	590.87[2]
Total Number of Deaths	27	27	27	27
Number with zero exposure	0	6	0	6
Number with Non-Zero Exposure below EC	27	21	1	1
Percentage of Deaths below EC	100%	100%	3.70%	25.93%

[1]Equivalent Occupational Exposure 70 years (ppm-days) = EC×(365/240)×(20/10)×365.25×(70-lag)
[2]The maximum occupational exposure concentration for lymphoid deaths was less than 326,106 ppm-days for the unlagged and 137,243 ppm-days for the 15-year lag exposure

Since the 95% lower confidence limit of the 1/100,000 effect concentration (LEC) was considered the most appropriate health protective point-of-departure, we extracted data from TCEQ (2019) that calculated the relevant cancer risk factors based on this same LEC. We then calculated the cancer URE and adjusted the URE by multiplying it by 1.66 to account for the same default age-adjusted default factor (ADAF) to derive a 1/M RSC value of 245 ppt (Tables 4 and 5).

We agree with the proposed MON amendment and the ORD (2019) sensitivity analysis that the central estimate should also be considered. When the MLE URE of 1.03E-03 per ppm is used to derive the URE, then the central estimate (maximum likelihood estimates) for the ADAF adjusted URE is 1.7E-03 per ppm. This value is 1.4 fold lower than the upper bound URE of 2.46 E-03 per ppm. The 1/M RSC value based on the central estimate is 585 ppt.

Table 4 Maximum likelihood estimate (MLE) of the slope parameter, standard error, and deviance (minus two times the log likelihood), and likelihood ratio test statistic corresponding to lymphoid cell line tumors mortality in male workers and both sexes combined

Cancer Outcome	MLE[1]	(SE)[1]	Deviance[1]: -2 × Ln (Likelihood)	Likelihood Ratio Test Statistic[1]	p-value[2] vs. null
Lymphoid Mortality Males only	3.12E-06	(2.61E-06)	356.553	1.052	0.3050
Lymphoid Mortality- Males and Females	2.81E-06	(2.65E-06)	727.899	0.860	0.3537

[1]Values extracted from TCEQ (2017) Tables 7 and 8
[2]p-value calculated based on pre-selecting lag at 15-years based on IRIS (2016) and not optimized to be more comparable to TCEQ Table 38 correction for IRIS (2016) which also did not consider lag as a parameter.

Table 5 MLE and 95% Lower confidence limit (95%LCL) for Cancer Risk Factors

Cancer Outcome	MLE Environmental Concentration 1/100,000 **ppm**	95% LCL Environmental Concentration (LEC) 1/100,000 **ppm**	MLE URE per **ppm**	95% UCL URE per **ppm**	ADAF adjusted 95% UCL URE (x 1.66) Per **ppb** (per ug/m^3)	ADAF adjusted 1/ M RSC ppt (ug/m^3)
Lymphoid Mortality Males only	9.67E-03	4.07E-03	1.03E-03	2.46E-03	4.1E-06 (2.2E-06)	**245 (0.45)**
Lymphoid Mortality Males & Females	1.32E-02	5.18E-03	7.57E-04	1.93E-03	3.2E-06 (1.8E-06)	312 (0.57)

Additional differences in our approach compared to the IRIS (2016) approach are listed in Table 6.

Table 6 Key sources of differences between Alternative Approach and EO IRIS Assessment Approach and rationale based on Valdez-Flores et al. (2010).

Valdez-Flores et al (2010) compared to EO IRIS Assessment	Reference and Rationale for Valdez-Flores et al (2010) approach	Approximate Factor[1]
Extra risk at age 70 instead of 85 years	Valdez-Flores et al. (2010), p. 319 Rationale: IRIS (2016) forces life-table analysis to 85 because of misunderstanding that the cut-off age represents age of life expectancy. Calculating extra risks through age 85 years makes the life table analysis unstable because <1% of cohort lived past 85 involving extrapolation of the fitted models beyond the range of the data upon which they are based. This introduces considerable uncertainty compared to analysis that calculates extra risk through 70 based on cohort information. (Valdez-Flores et al. 2010)	2.3
Extra risk using background rates instead of background mortality rates with lymphoid mortality data (incidence/mortality ratio, $R_{i/m}$).	$R_{i/m}$ = 5.26/1.99 (Valdez-Flores et al. 2010) Rationale: IRIS used the lymphoid mortality model and then applied incorrect assumptions and formulas based on incidence inappropriate for mortality that may significantly alter the exposure-response. The alternative approach relies on original mortality data and assumptions appropriate for mortality (Sielken and Valdez-Flores et al 2009)	2.64

[1]Factor is based on comparison of 0-lag CPH model, so the factor may be slightly different for 15-yr lag CPH model

In summary, our approach results in a 1/M RSC of 245 ppt for the general population including children, and is biologically plausible based on animal data and background levels (predominately endogenous levels) and variability of EtO in humans. This approach is conservative because (a) extra risk was calculated despite no statistically significant slope in the exposure-response analyses; (b) no adjustment was made for likelihood of underestimation of exposures (Bogen et al. 2019[9]); (c) the limited evidence of cancer risk based on the entire body of epidemiologic evidence (Marsh et al. 2019) and in the NIOSH cohort (Steenland et al. 2003, 2004) and (d) the 1/M RSC value of 245 ppt is still substantially below endogenous levels and well within the population variability of endogenous levels.

[9] See ACC comments on the proposed HCl RTR rule

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Attachment A

Request for Correction Submitted by ACC to EPA on September 20, 2018

Attachment B

ACC EO Panel Comments on EPA Proposed Amendments to "National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review", April 2019

Attachment C

ACC EO Panel Comments on the TCEQ Proposed Development Support Documents (DSDs) for Ethylene Oxide (EtO) Carcinogenic Dose-Response Assessment, September 2019